

WHAT IS CLAIMED IS:

Sub C 1

5 1. A method to identify an agent that alters adeno-associated virus transduction of a mammalian cell, comprising:  
a) contacting the mammalian cell with the agent and virus; and  
b) detecting or determining whether virus transduction is altered.

Sub D 1

10 2. The method of claim 1 wherein the cell is a mammalian lung cell.  
3. The method of claim 1 wherein the cell is a mammalian liver cell.

15 4. The method of claim 1 wherein the cell is a human cell, canine cell, murine cell, rat cell or rabbit cell.  
5. The method of claim 1 wherein the transduction is enhanced.

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20 6. The method of claim 1 wherein endosomal processing is enhanced.  
7. The method of claim 1 wherein the agent is an endosomal protease inhibitor.  
8. The method of claim 7 wherein the agent is a cysteine protease inhibitor.

Sub D 1

25 9. The method of claim 1 wherein the agent is a peptide or analog thereof.  
10. The method of claim 1 wherein the virus is recombinant adeno-associated virus.

30 11. The method of claim 10 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.  
12. The method of claim 10 wherein the recombinant virus comprises a marker gene or a selectable gene.

Sub C 11

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13. A method to alter adeno-associated virus transduction of a mammalian lung cell, comprising: contacting the mammalian lung cell with an amount of an agent and an amount of virus effective to alter virus transduction.

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14. A method to alter adeno-associated virus transduction of a mammalian liver cell, comprising: contacting the mammalian liver cell with an amount of an agent and an amount of virus effective to alter virus transduction.

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15. A method to alter the expression of a transgene in a mammalian lung cell, comprising: contacting the mammalian lung cell with an amount of an agent and an amount of recombinant adeno-associated virus comprising the transgene so as to alter expression of the transgene.

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16. A method to alter the expression of a transgene in a mammalian liver cell, comprising: contacting the mammalian liver cell with an amount of an agent and an amount of recombinant adeno-associated virus comprising the transgene so as to alter expression of the transgene.

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17. A method comprising: contacting a mammal subjected to gene therapy with recombinant adeno-associated virus comprising a transgene with an amount of an agent effective to alter expression of the transgene in the cells of the mammal.

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18. The method of claim 13, 14, 15, 16, or 17 wherein endosomal processing of the virus is altered.

19. The method of claim 13 or 14 wherein the virus is recombinant adeno-associated virus.

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20. The method of claim 19 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.

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21. The method of claim 13 or 14 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.

22. The method of claim 15, 16, or 17 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.

23. The method of claim 13, 14, 15, 16 or 17 wherein the cell is contacted with the agent before the cell is contacted with the virus.

24. The method of claim 13, 14, 15, 16 or 17 wherein the cell is contacted with the virus before the cell is contacted with the agent.

25. The method of claim 13, 14, 15, 16 or 17 wherein virus transduction is enhanced.

26. The method of claim 15, 16 or 17 wherein transgene expression is enhanced.

27. The method of claim 17 wherein expression is altered in lung cells.

28. The method of claim 17 wherein expression is altered in liver cells.

29. The method of claim 1, 13, 14, 15, 16 or 17 wherein the agent is a compound of formula (I):  $R_1-A-(B)_n-C$  wherein  $R_1$  is an N-terminal amino acid blocking group; each A and B is independently an amino acid; C is an amino acid wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and n is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof.

30. The method of claim 29 wherein  $R_1$  is  $(C_1-C_{10})$  alkanoyl.

31. The method of claim 29 wherein  $R_1$  is acetyl or benzyloxycarbonyl.

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32. The method of claim 29 wherein each A and B is independently alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine.

33. The method of claim 29 wherein each A and B is isoleucine.

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34. The method of claim 29 wherein C is alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.

10 35. The method of claim 29 wherein C is nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.

36. The method of claim 29 wherein R<sub>1</sub> is (C<sub>1</sub>-C<sub>10</sub>)alkanoyl or benzyloxycarbonyl; A and B are each isoleucine; C is nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and N is 1.

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37. The method of claim 1, 13, 14, 15, 16 or 17 wherein the agent is a compound of formula (II):

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wherein

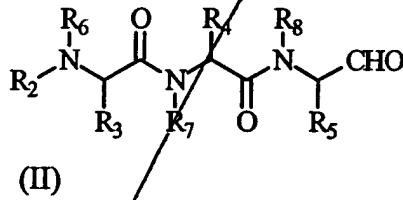
R<sub>2</sub> is an N-terminal amino acid blocking group;

R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are each independently hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl, aryl or aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; and

R<sub>6</sub>, R<sub>7</sub>, and R<sub>8</sub> are each independently hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; or a pharmaceutically acceptable salt thereof.

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38. The method of claim 37 wherein R<sub>2</sub> is (C<sub>1</sub>-C<sub>10</sub>)alkanoyl.



39. The method of claim 37 wherein  $R_2$  is acetyl or benzyloxycarbonyl.

40. The method of claim 37 wherein  $R_3$  is hydrogen or  $(C_1-C_{10})$ alkyl.

5 41. The method of claim 37 wherein  $R_3$  is 2-methylpropyl.

42. The method of claim 37 wherein  $R_4$  is hydrogen or  $(C_1-C_{10})$ alkyl.

43. The method of claim 37 wherein  $R_4$  is 2-methylpropyl.

10 44. The method of claim 37 wherein  $R_5$  is hydrogen or  $(C_1-C_{10})$ alkyl.

45. The method of claim 37 wherein  $R_5$  is butyl or propyl.

15 46. The method of claim 37 wherein  $R_2$  is acetyl or benzyloxycarbonyl;  $R_3$  and  $R_4$  are each 2-methylpropyl;  $R_5$  is butyl or propyl; and  $R_6$ ,  $R_7$ , and  $R_8$  are each independently hydrogen.

20 47. The method of claim 1, 13, 14, 15, 16 or 17 wherein the agent is a compound of formula (III):

wherein

$R_1$  is H, halogen,  $(C_1-C_{10})$ alkyl,  $(C_1-C_{10})$ alkenyl,  $(C_1-C_{10})$ alkynyl,  $(C_1-C_{10})$ alkoxy,  $(C_1-C_{10})$ alkanoyl,  $(=O)$ ,  $(=S)$ , OH, SR, CN,  $NO_2$ , trifluoromethyl or  $(C_1-C_{10})$ alkoxy, wherein any alkyl, alkenyl, alkynyl, alkoxy or alkanoyl may

25 optionally be substituted with one or more halogen, OH, SH, CN, NO<sub>2</sub>, trifluoromethyl, NR<sub>2</sub> or SR, wherein each R is independently H or (C<sub>1</sub>-C<sub>10</sub>)alkyl;

R, is (=O) or (=S);

R<sub>3</sub> is H, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)alkenyl, (C<sub>1</sub>-C<sub>10</sub>)alkynyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy or (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO<sub>2</sub>, trifluoromethyl, SR, or NRR, wherein each R is independently H or (C<sub>1</sub>-C<sub>10</sub>)alkyl;

R<sub>4</sub> is H, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)alkenyl, (C<sub>1</sub>-C<sub>10</sub>)alkynyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy or (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO<sub>2</sub>, trifluoromethyl, SR, or NRR, wherein each R is independently H or (C<sub>1</sub>-C<sub>10</sub>)alkyl;

10 C<sub>1</sub>-C<sub>10</sub>)alkyl;

R<sub>5</sub> is H, halogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)alkenyl, (C<sub>1</sub>-C<sub>10</sub>)alkynyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, (C<sub>1</sub>-C<sub>10</sub>)alkanoyl, (=O), (=S), OH, SR, CN, NO<sub>2</sub> or trifluoromethyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or alkanoyl may optionally be substituted with one or more halogen, OH, SH, CN, NO<sub>2</sub>, trifluoromethyl, NRR or SR, wherein each R is independently H or (C<sub>1</sub>-C<sub>10</sub>)alkyl; and

X is O, S or NR wherein R is H or (C<sub>1</sub>-C<sub>10</sub>)alkyl, or a pharmaceutically acceptable salt thereof.

48. The method of claim 47 wherein R<sub>1</sub> is halogen, CN, NO<sub>2</sub>, trifluoromethyl or OH.

49. The method of claim 47 wherein R<sub>1</sub> is OH.

50. The method of claim 47 wherein R<sub>2</sub> is (=O).

51. The method of claim 47 wherein R<sub>3</sub> is H or (C<sub>1</sub>-C<sub>10</sub>)alkyl.

52. The method of claim 47 wherein R<sub>3</sub> is methyl.

30 53. The method of claim 47 wherein R<sub>4</sub> is H or (C<sub>1</sub>-C<sub>10</sub>)alkyl.

54. The method of claim 47 wherein R<sub>4</sub> is H.

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55. The method of claim 47 wherein  $R_5$  is halogen, CN,  $NO_2$ , trifluoromethyl or OH.

56. The method of claim 47 wherein  $R_5$  is OH.

57. The method of claim 47 wherein X is O or S.

58. The method of claim 47 wherein X is O.

10 59. The method of claim 47 wherein both ----- are a single bond.

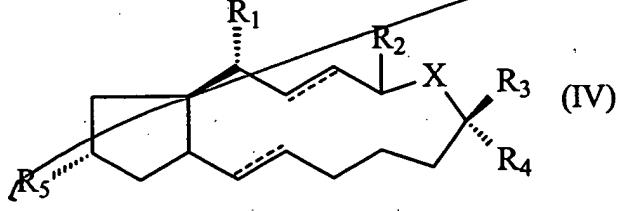
60. The method of claim 47 wherein one ----- is a double bond.

61. The method of claim 47 wherein both ----- are a double bond.

15 62. The method of claim 45 wherein  $R_1$  is OH,  $R_2$  is (=O),  $R_3$  is methyl,  $R_4$  is H,  $R_5$  is OH, X is O, and both ----- are a double bond.

Sub B' 63. The method of claim 44 wherein the compound is a compound of formula (IV):

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64. The method of claim 63 wherein  $R_1$  is halogen, CN,  $NO_2$ , trifluoromethyl or OH.

25 65. The method of claim 63 wherein  $R_1$  is OH.

66. The method of claim 63 wherein  $R_2$  is (=O).

67. The method of claim 63 wherein  $R_3$  is H or  $(C_1-C_{10})$ alkyl.

68. The method of claim 63 wherein  $R_3$  is methyl.

69. The method of claim 63 wherein  $R_4$  is H or  $(C_1-C_{10})$ alkyl.

5 70. The method of claim 63 wherein  $R_4$  is H.

71. The method of claim 63 wherein  $R_5$  is halogen, CN,  $NO_2$ , trifluoromethyl or OH.

10 72. The method of claim 63 wherein  $R_5$  is OH.

73. The method of claim 63 wherein X is O or S.

74. The method of claim 63 wherein X is O.

15 75. The method of claim 63 wherein both ----- are a single bond.

76. The method of claim 63 wherein one ----- is a double bond.

20 77. The method of claim 63 wherein both ----- are a double bond.

78. The method of claim 63 wherein  $R_1$  is OH,  $R_2$  is (=O),  $R_3$  is methyl,  $R_4$  is H,  $R_5$  is OH, X is O, and both ----- are a double bond.

a 25 79. The method of claim 1, 13, 14, 15, 15 or 17 wherein the agent inhibits the activation of ubiquitin, the transfer of ubiquitin to the ubiquitin carrier protein, ubiquitin ligase, or a combination thereof.

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a 30 80. The method of claim 1, 13, 14, 15, 15 or 17 wherein the agent inhibits ubiquitin ligase.

a 81. The method of claim 1, 13, 14, 15, 15 or 17 wherein the agent is a compound of formula (IV):



wherein R is hydrogen, an amino acid, or a peptide, wherein the N-terminus amino acid can optionally be protected at the amino group with acetyl, acyl, trifluoroacetyl, or benzyloxycarbonyl; A is an amino acid or a direct bond; A<sub>1</sub> is an amino acid; and

5 a direct bond; A<sub>1</sub> is an amino acid; and

R<sub>1</sub> is hydroxy or an amino acid, wherein the C-terminus amino acid can optionally be protected at the carboxy group with (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl, benzyl ester or amide (e.g., C(=O)NR<sub>2</sub>, wherein each R is independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl);

10 or a pharmaceutically acceptable salt thereof.

82. The method of claim 81 wherein the agent is H-Leu-Ala-OH, H-His-Ala-OH, or a combination thereof.

15 83. The method of claim 1, 13, 14, 15, 15 or 17 further comprising  
administering a second agent that enhances the activity of the agent.

84. The method of claim 83 wherein the second agent is EGTA.

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